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08/644,289	05/10/96	KULESZ-MARTIN	M	RPP:135D-US

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DUNN AND ASSOCIATES
P O BOX 96
NEWFANE NY 14108

EXAMINER	
EYLER, Y	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/644,289	Applicant(s) Kulsz-Martin
	Examiner Yvonne Eyler	Group Art Unit 1642

☒ Responsive to communication(s) filed on *Feb 20, 1998* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 3-6, and 8-18* is/are pending in the application.

Of the above, claim(s) *12-14* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 3-6, 8-11, and 15-18* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 1, 3-6, and 8-18 are pending in the application. Claims 12-14 have been withdrawn from further consideration. Claims 1, 3-6, 8-11, and 15-18 are under consideration.

Claim Rejections Withdrawn:

3. The rejection of Claims 1, 3, 4 and 15 under 35 U.S.C. 102(b) as being anticipated by Han et al (IDS; Nuc.Acids Res. 20:1979-1981, 1992) is withdrawn.

Claim Rejections Maintained and New Grounds of Rejection:

4. The rejection of Claims 1, 3-6, 8-11 and 15 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

The recitation ""functionally equivalent to active p53" is maintained to be vague and indefinite. Applicant quotes passages from pages 2 to 3 of the specification describing that growth regulatory function of p53as is maintained and equivalent to that of mouse p53as and p53. The specification also states that in general p53as functions the same as p53. However, these "functions" are not defined. There is no definition of "active p53." There is no definition of what measurable "actions", "functions" etc. are definitive of "active p53." Without such, it is not clear what is equivalent to "active p53 function" and what is not. Indeed, the specification teaches that

antigenic function (i.e. binding to Ab421 and Ab122) is lost in p53as and suggests that additional cellular functions are gained. (See page 1). Thus, if one were to consider only antigenic function, for example, the instant p53as protein would not be identified.

All other bases of rejection under 112 second are withdrawn in light of the amendments to the claims.

It is noted that sequence I.D. No. should be in all caps, i.e. SEQUENCE I.D. NO.

It is also noted that in the last line of claims 1 and 5, "p53as" has inadvertently been changed to "p53" although this is not entered as an amendment and appears to be a typographical error. Clarification of this is requested. Absent a definite amendment, the claims will be interpreted to still read "p53as."

Finally, the removal of the intron 10 language is acknowledged, and removes the indefiniteness and confusion regarding the presence of intronic material, which is known in the art to be nontranslated, in presumably wildtype p53 protein.

5. The rejection of Claims 1 and 5 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained.

With regard to Intron 10, and inactivating the negative regulatory region, the rejection is withdrawn in light of the amendments to the claims.

The rejection based on providing an epitope which gives rise to antibody specific for p53as is, however, maintained. Applicant points to pages 6-7 and page 8 of the specification in support of the claim limitation. The specification at page 8 and Table 1 does disclose a single antibody raised to a single epitope (residues 364-381 of an unspecified sequence, but presumably corresponds to SEQ ID NO: 1) but does not disclose or contemplate the breadth of the invention as now claimed. The claim is drawn to any modification that results in any epitope that gives rise to a p53as specific antibody. The requirements of the modifications and characteristics of this broadly claimed sequence and resulting epitope are not disclosed or contemplated within the specification at the date of filing.

6. The rejection of Claims 1, 3-6, 8-11 and 15 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

The basis of the rejection is that while the specification is enabling for plasmids containing a cDNA sequence which encodes a protein designated p53as, which is truncated by 9 amino acids, disrupting the negative regulatory region and the addition of 17 amino acids (SEQ ID NO: 1) from Intron 10; is not enabling for any plasmid containing a cDNA encoding any C-terminally modified p53 protein designated p53as.

Applicant continues to argue that the specification clearly teaches that modification of the C-terminus can be used to eliminate the regulatory domain and that the advantages of a unique C-

terminal epitope are also clearly taught. Applicant maintains that since the techniques used to accomplish such modifications are art-standard, that the specification fully describes and enables the scope of the claimed invention.

These arguments have been considered but are not found to be persuasive for reasons of record and as detailed below.

Initially, it is noted, as discussed supra, that the instant specification is not found to clearly teach or contemplate the modification of the C-terminus to include any unique epitope, nor are advantages of doing such taught. There is no description of unique epitope tags and their addition to p53 other than the 17 amino acids from the alternative splicing of Intron 10. Neither is sufficient guidance found regarding the acceptable locations within the C-terminus where modifications to add epitope tags may be accomplished without functionally changing the molecule itself. Similarly, there is insufficient guidance regarding the size and structure of modifications which the p53 molecule will tolerate without functional change. Additionally, the specification does not provide guidance regarding extent of truncation and location that will be tolerated by the p53 protein without functional change other than elimination of the negative regulatory domain. As made of record, the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be deleted and substituted within a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Furthermore, the activities which determine

"function" are not clearly set forth or claimed as discussed supra, nor are the structural/functional relationships which maintain definable functions set forth. Therefore, the predictability of functional equivalence, elimination of negative regulation, and gain of unique epitopic properties as a result of any truncation and substitution within the C-terminus as not been established. Thus, while recombinant techniques are available and known in the art, it is not routine in the art to screen large numbers of substituted proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. It is maintained that it would require undue experimentation by one of skill in the art to practice the invention as claimed without further guidance from the instant specification.

7. New Claims 16-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons detailed above and of Record regarding claims 1, 3-6, 8-11 and 15.

New claim 16 merely recites that sequence contain a portion of SEQ ID NO: 1which raises antibodies. Note that the antibodies raised are not limited to those specific for SEQ ID NO: 1 or for p53as protein and thus encompass any portion of SEQ ID NO: 1. New claims 17 and 18 depend from claims 1 and 5 but do not overcome the stated enablement issues above.

8. The rejection of Claims 1, 3, 4, and 15 under 35 U.S.C. 102(b) as being anticipated by Wolf et al (IDS; Mol. Cell Biol. 5:127-132, 1985) is maintained as evidenced by Arai et al.

9. The rejection of Claims 1,3, 4 and 15 under 35 U.S.C. 102(b) as being anticipated by Arai et al (IDS; Mol. Cell Biol. 6:3232-3239, 1986) is maintained.

Applicants arguments with regard to Wolf et al and Arai et al will be addressed together.

The main issue is wether the invention was described in a printed publication more than one year prior to the date of the instant application based on the publication of the plasmid M-8 containing a cDNA sequence encoding a p53as.

Applicant asserts that the rejection of Claims 1, 3, 4, and 15 under 35 U.S.C. 102(b) as being anticipated by Wolf et al (IDS; Mol. Cell Biol. 5:127-132, 1985) as evidenced by Arai et al. is improper because it is a combination of references which does not cite inherent properties. This is not found to be persuasive. Wolf et al. teaches the M-8 plasmid. Arai et al. is cited **as evidence** only regarding the properties of the M-8 plasmid.

Applicant argues that the M-8 plasmid does not anticipate the instant plasmid because the encoded protein is not contemplated to be functionally equivalent to active p53 and the cDNA was obtained from transformed cells. Further, applicant argues that the sequence of the M-8 cDNA is not the same as p53, citing a cys to phe substitution at residue 132.

These arguments have been considered but are not found to be persuasive. The activities that define functional equivalency have not been clearly set forth as discussed supra. The cloned p53 cDNA molecule described by Wolf et al. and Arai et al. appears, however, to be functionally equivalent to "active p53" encompassed by the term. Wolf et al. teach that transfection with M-8 reconstitutes expression of p53, changing the phenotype of the transfected cells, the resulting

protein differing from active p53 only immunologically (see column 1, page 127 of Wolf et al. and column 1, page 3232 of Arai et al.). Furthermore, Arai et al. teach that the isolation of the M-8 cDNA "suggests that the single **functional p53 gene of the mouse** is coding for at least two p53 mRNA species...," thus indicating that M-8 encodes a functionally equivalent p53, only differing by the alternative splicing instantly at question. Applicant infers that the cDNA of M-8 transforms cells and forms monomers and dimers rather than tetramers, but fails to supply objective evidence regarding this unclaimed characteristic and does not provide the referenced journal articles. Finally, applicant asserts that the p53as of Wolf et al. and Arai et al. differs from the instant because it was isolated from transformed cells. The origin of the claimed cDNA does not affect the identity of the compound itself, however, it is noted that the instant specification teaches that p53as is found both in transformed cells and in normal cells (page 1). Thus, all available objective evidence indicates that the cDNA of M-8 is functionally equivalent to active p53 within the meaning encompassed by the limitation and meets the limitations of the claimed plasmid.

Applicant also asserts that the sequence of the cDNA of M-8 differs from the instant p53as and from "active p53." Arai et al. teaches that the M-8 sequence differs from the cDNA contained in plasmid M11 at three locations in addition to the alternative splicing. Arai et al. also teaches that only one difference exits between the M-8 sequence and the cDNA found in plasmid pCD-p53. Both p53 proteins encoded by M11 and pCD-p53 presumably are "active p53s," but both differ sequentially from each other. There is no consensus sequence provided for "active p53" nor for the instant p53as molecule. Since the art indicates that p53as is functionally

equivalent to active p53, and absent evidence to the contrary regarding "active p53" and M-8, it would appear to be sequentially the same as active p53 within the scope encompassed by the claims and meets the limitations of the claimed plasmid.

10. New Claims 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolf et al (IDS; Mol. Cell Biol. 5:127-132, 1985) as evidenced by Arai et al for reasons of record as applied to claims 1, 3, 4, and 15.

Claims 16 and 17 merely recite 17 amino acid sequence from intron 10 which is inherently part of the cDNA of M8 and the transfection of host cells with the plasmid which is also taught by Wolf et al..

11. New Claims 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Arai et al (IDS; Mol. Cell Biol. 6:3232-3239, 1986) for reasons of record as applied to claims 1, 3, 4, and 15.

Claims 16 and 17 merely recite 17 amino acid sequence from intron 10 which is inherently part of the cDNA of M8 and the transfection of host cells with the plasmid which is also taught by Arai et al.

12. Claims 1, 3-6, 8-11 and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolf et al (Mol. Cell Biol. 5:127-132, 1985) as evidenced by Arai et al. or Arai et al (Mol. Cell Biol. 6:3232-3239, 1986) as set forth above regarding claims 1, 3, 4, and 15, in view of Lee et al (IDS; EP 529160).

Wolf et al. and Arai et al. set forth as detailed above and in the Office Actions of 3/28/97 and 10/15/97. Wolf et al. and Arai et al. differ from the instantly claimed invention only in that the cDNA of M-8 is not cloned into a viral vector.

Applicant argues that Wolf et al. and Arai et al. do not disclose cDNA encoding p53as which is not found to be persuasive as detailed above. Further, applicant argues that none of the cited references suggest cloning the cDNA of Wolf et al. or Arai et al. into a viral vector and the technical feasibility of such cloning does not render it obvious. This has been considered but is not found to be persuasive. Both Wolf et al. and Arai et al. suggest the need for further investigation of the role of p53as proteins in malignancy (See Wolf et al. page 131 and Arai et al. page 3238) while Arai et al. further teaches that the availability of cloned cDNA facilitates further investigation (page 3238). Lee et al. teaches the importance of gene products and the advantages of a mechanism to obtain intact, biochemically active protein in large quantities to advance investigation of the properties of that protein. (See page 2, lines 40-45). Lee et al. teach the cloning of cDNA into viral vectors to accomplish this advantage. Thus, not only does Lee et al. teach the technical feasibility of a reasonable expectation of success, Lee et al. also teaches a motivation to do so, i.e. to obtain large quantities of protein for investigation. Both Wolf et al. and Arai et al. teach the desirability to further elucidate the properties of p53as protein. Finally, it is not necessary that the claimed invention be expressly suggested in any one or all of the references to justify combining their teachings; rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art *In re Keller,* 642 F.2d

413, 288 USPQ 871 9 CCPA 1981). Therefore, given the known desirability to obtain and investigate p53as function and the known advantages of Lee et al's teachings to advancement of the study of specific gene products, it is maintained that it would have been *prima facie* obvious to one of ordinary skill in the art to clone the cDNAs of plasmid M-8 taught by Wolf et al. or Arai et al. into viral vectors with a reasonable expectation of success and one would have been motivated to do so to obtain large amounts of gene product as taught by Lee et al. which would be desirable for elucidation of properties of p53as.

13. Claims 1, 3-6, 8-11 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al (Nuc.Acids Res. 20:1979-1981, 1992), in view of Lee et al (IDS; EP 529160).

Han et al. teach as set forth in the Office Actions of 3/28/97 and 10/15/98. Han et al. teach that existence of alternatively spliced RNA of p53, meeting the requirements of the instant p53as- i.e. C-terminal truncation of 9 amino acids and addition of 17 amino acids from Intron 10, is present in both normal and transformed cells and suggest that it's presence may be universal. See the abstract and page 1981. Indeed, the instant specification acknowledges the prior art knowledge of the existence of p53as and cites Han et al. Further, Han et al. use the art-known knowledge of the differences between p53as cDNA and other p53 species of cDNA to clone segments of p53as cDNA into plasmids and demonstrate the ubiquitous existence of p53as. Finally, Han et al. teach that more precise biochemical and biological characterization of p53as properties is critical in future studies of normal and oncogenic cells. See page 1981. Han et al.

differ from the instant invention, as applicant has successfully argued, by not teaching the cloning of full length p53as cDNA encoding p53as protein into plasmids or viral vectors.

The cloning of cDNA into plasmids, is however, art standard technique and is indeed taught by Han et al. Further, Han et al. provide primers and methods of determining the successful cloning of p53as cDNA product based on known C-terminal differences. Han et al. also provide a motivation to obtain and study full length p53as cDNA, stating that more precise characterization of p53as properties is critical to normal and oncogenic cell study.

Lee et al, as discussed supra, teach the advantages of obtaining large quantities of gene product and teach that cloning of cDNA into viral vectors accomplishes just that.

Applicant has argued that there is no motivation to clone full length p53as cDNA encoding p53as protein into either plasmids or viral vectors based on the teachings of Han et al. and Lee et al. This is not found to be persuasive, as discussed above, because Han et al. teach the desirability, indeed criticality, for further characterization of p53as and Lee et al. teach the advantages of cloning into viral vectors instead of plasmids.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to clone p53as cDNA, known in the art as taught by Han et al., into either plasmids or viral vectors with a reasonable expectation of success to characterize the precise properties of the encoded p53as protein.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvonne Eyler, Ph.D. whose telephone number is (703) 308-6564. The examiner can normally be reached on Monday through Friday from 830am to 630pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-2731. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**paula.hutzell@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Yvonne Eyler, Ph.D.
February 8, 1999